DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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Subject Information for November 12-13 Meeting of Risk Communication Advisory Committee

To Members, Risk Communication Advisory Committee

FDA's Risk Communication Advisory Committee will hold its next meeting on November 12 and 13, 2009, to discuss three topics:

- Update on Transparency Task Force
- Communication to the Public via NIH Clinical Trials Database
- Briefing of the RCAC about the new Center for Tobacco Products

This memo is to provide background in preparation for the meeting.

Transparency Task Force – Background

The Federal Register Notice about the November 3, 2009, Transparency Task Force Public Meeting may be helpful along with other materials from the FDA Transparency Task Force Website: www.fda.gov/transparency.

As you prepare for the meeting, please consider the general topic of early communication about emerging safety issues concerning FDA-regulated products. The following two hypothetical situations may help start the discussion of the issue, but please note that our interest is in communication of emerging information in general, not the specifics of the hypothetical examples.

First Hypothetical Case Study: Early Communication about Emerging Safety Issues about FDA-Regulated Products

> State and local public health authorities have been investigating an outbreak due to a foodborne pathogen. There are 18 illnesses primarily in one state with a few in a neighboring state. According to the human laboratory data, the same strain of pathogen caused all of the illnesses. One individual has died. The epidemiological investigation by the states found sandwiches and salads in common but no epidemiologic study is underway yet to implicate a specific food item.

- Should FDA communicate this outbreak to the public? If so, what should the agency say? Is there anything that should not be communicated?
- Should knowledge of the specific pathogen causing the outbreak influence the agency's decision?
- Should the population that may be potentially exposed to the pathogen affect whether, and when, a message should be communicated?
- How should FDA effectively communicate to consumers as the investigation evolves and new information changes the picture?

Second Hypothetical Case Study: Early Communication about Emerging Safety Issues about FDA-Regulated Products

There is an outbreak of a foodborne pathogen with 50 people ill in five states, many of whom have been hospitalized. State and local epidemiologists and CDC are investigating the human illnesses.

CDC alerts FDA that the epidemiological investigation conducted shows a link to fresh fruit salad consumed at various restaurants. Although recipes varied at the restaurants, three fruits were common to all of the salads consumed. Preliminary data suggests that cantaloupe is the cause. FDA contacts industry and they provide general distribution information indicating that cantaloupe is typically distributed nationwide. FDA has initiated a traceback of cantaloupe.

Produce trade associations have asked FDA and CDC for the information the agency has gathered about the source of the outbreak. These associations tell the agency that they can assist with the investigation if the agency provides them with more information about the outbreak.

(Note: Because the purpose of the discussion is to elucidate the policy considerations that should be weighed in deciding whether changes to current practice, laws, or regulations are warranted, the issues should be discussed without regard for the current practice, laws, or regulations.)

- Should FDA advise the public about this outbreak? What are the factors that should be considered in deciding whether to do so? Is there anything that should not be communicated?
- If the agency communicates to the public about the outbreak, what message should be communicated to consumers? What geographic area should be covered?
- Should FDA communicate to members of industry whose products may be implicated in the outbreak? If so, what is the message?
- How should FDA work with industry to address the outbreak?
- Another entity, based on its own analyses, believes the outbreak is due to another fruit and releases a public statement to that effect. How should the agency respond?

Clinical Trials Database – Background

The second topic of the advisory committee meeting is related to a part of the FDA Amendments Act (FDAAA), or Public Law 110-85, that we have not discussed at length with this committee. Title VIII of the FDAAA provides for expansion of the information posted in the NIH clinical trials registry and results database, ClinicalTrials.gov.

NIH is responsible for managing ClinicalTrials.gov, but FDA is responsible for enforcement of statutory requirements related to submission of registration and results information and submission of certain information to FDA (e.g., certification of compliance). Title VIII calls for “responsible parties” (sponsors or designated principal investigators) to register in the database “applicable clinical trials” of FDA-regulated drugs, biologics, and devices. For completed applicable clinical trials involving approved products, Title VIII also calls (starting in September 2008) for the submission of basic results information, which includes baseline characteristics of the subjects (such as age and sex), and primary and secondary outcomes. Starting in September 2009, data on serious and other adverse events was also required to be submitted. Both basic results information and adverse events

information are posted at ClinicalTrials.gov in a tabular format. In consultation with risk communication experts (though the source of the experts is not specified), additional information may be posted to make the tables more understandable to members of the public.

NIH received many comments in response to a public meeting held in April 2009 on issues associated with further expansion of ClinicalTrials.gov (e.g., results reporting for trials of unapproved products, submission of narrative summaries of results). You can review any of the comments, if you wish, by visiting www.regulations.gov, and entering the docket number "NIH-2009-0002" as the keyword or ID.

Here are some more links that may be helpful in your preparation for the meeting:

For the database, first see http://ClinicalTrials.gov.

You may also find the following link helpful; it leads to a current listing of the ClinicalTrials.gov Results Records:
http://www.clinicaltrials.gov/ct2/results?term=%28+NOT+NOTEXT+%29+%5BFIRST-RECEIVED-RESULTS-DATE%5D

Finally, at the following link you can find more information about the law itself and the data base: http://prsinfo.clinicaltrials.gov/fdaaa.html (see especially, the "Expanded Registry" and "'Basic Results' Database" sections)

In addition to the links, NIH experts have suggested some articles that may be of interest:

Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest*. 2009 Jul;136(1):295-303. http://chestjournal.chestpubs.org/content/136/1/295.full.pdf

Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. *Science*. 2008 Mar 7;319(5868):1340-2. http://www.sciencemag.org/cgi/reprint/319/5868/1340.pdf

Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. *JAMA*. 2007 May 16;297(19):2112-20. http://jama.ama-assn.org/cgi/reprint/297/19/2112.pdf
(please note that this article predates the enactment of FDAAA Title VIII)

As you prepare for the meeting, please consider the following topics. We look forward to hearing your reactions in discussion at the meeting.

- How can we enhance public understanding of the limitations (listed below) of the trial-level data in the Results Database and minimize misinterpretation or inappropriate use of the data for purposes of health care decision-making? Some of the key concepts that need to be effectively communicated are:
    - Data in ClinicalTrials.gov come from individual trials only and do not reflect the totality of relevant information about the topic at hand
    - Adverse events reported may or may not be caused by the intervention(s) under study
    - Trial and results information posted at ClinicalTrials.gov has not been reviewed or validated by NIH or FDA; in other words, the trial may or may not have internal or external validity for the questions that it is addressing
    - Results may or may not be statistically significant (or clinically relevant); even if statistical analyses are provided, they may or may not be appropriate

- The tables of results data (including adverse events) at ClinicalTrials.gov are likely to be more comprehensible to individuals with clinical research expertise than to the lay public. What types of additional information would enhance public understanding of the results information and the context in which it must be considered? What are the effective ways of providing such information?

- Considering the public display of clinical trial results, as currently presented in ClinicalTrials.gov, particularly outcome measure and adverse event information, should results information be displayed differently for the lay public? For example, should users be led through background information prior to seeing the results posted for a specific trial? If so, how could that information be best organized to assist members of the public in properly understanding the utility of the results of a single trial, taking into account the key concepts outlined in the first bullet above?

FDA's Center for Tobacco Products – Background

The third topic is primarily an informational briefing about the new Center for Tobacco Products. Following is a link to a recent Q&A that may be helpful:
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm183919.htm

We all are looking forward to a very interesting meeting. Please do not hesitate to contact me if I can be of any help. Best wishes for safe and pleasant travels.